IN THE SPECIFICATION:

Please replace the paragraph beginning at page 11, line 8, with the following rewritten paragraph:

Figures 6A-6D. A critical 18 nucleotide sequence within the 57 nucleotide ISAR sequence between Nde I and Nsi I nearly restores splicing regulation in DT3 cells. (Fig. 6A) The 57 nucleotide ISAR sequence is indicated at the top and deletions and mutants of this sequence are shown as are control pBluescript sequences. The 18 nucleotide "core sequence" (Rep1) is boxed, and mutant sequences are underlined and in boldface. All sequences were tested by deleting ISAR sequences from pI-11-FS/Not/Cla-ISAR and inserting the indicated sequences (SEQ ID NOs: 34-44). (Fig. 6B) SAR-20 and SAR 3' sequences restore regulation, whereas SAR 5' does not. (Fig. 6C) Mutations in the 18 nucleotide sequence shared by SAR-20 and SAR 3' (Mut 2 and Mut 3) cause loss of regulation whereas a mutation outside this region (Mut 1) preserves regulation. (Fig. 6D) One or three copies of the 18 nucleotide "core sequence" restore splicing regulation, with three repeats of the sequence being slightly more

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efficient than one repeat. Abbreviations are defined in descriptions of Figs. 2 and 3.

Please replace the paragraph beginning at page 12, line 11, with the following rewritten paragraph:

Figures 8A and 8B. Intron sequences important for regulation of rat and human FGF-R2 splicing display are highly similar. (Fig. 8A) Rat intron sequences corresponding to previously reported 21 nucleotide human sequence, IAS 2, which also mediates IIIb activation contain only one nucleotide difference (SEQ ID NOs: 45 and 46, respectively). (Fig. 8B) The 57 nucleotide rat ISAR sequence is highly similar to human sequences (SEQ ID NO: 47) in this same region, including the 18 nt shown to be most important for regulation (boxed sequences).

Please replace the paragraph beginning at page 13, line 10, with the following rewritten paragraph:

Figure 10. Rat FGF-R2 intron between exons IIIb and IIIc (SEQ ID NO:48).

Please replace the paragraph beginning at page 13, line 12, with the following rewritten paragraph:

Figure 11. Human FGF-R2 intron between exons IIIb and IIIc (SEQ ID NO:49).

Please replace the paragraph beginning at page 18, line 13, with the following rewritten paragraph:

Plasmid Construction. The pPIP11 adenoviral splicing construct is based on the L1 and L2 exons and is similar to the previously described pPIP7A, except that the sequence of the 3' exon between the Pst I sites and Hind III sites has been replaced by the sequence 5'-CTGCAGGACAAACTCTTCGCGGTCTCTATGCATCCTCCGAACGGTAAGACCCTAAG CTT-3' (SEQ ID NO:1). The sequences of pPIP11 were PCR amplified with primers PIP10-F (5'-CCCGGGGGTACCGGGCGAATTCGAATT CGAGCTCACTC-3') (SEQ ID NO:2) and PIP11-R (5'-CCCGGGACTAGTAAGCTTAGGCT CTTGGCGTT-3') (SEQ ID NO:3). The PCR product was digested with EcoR1 and Spe I and inserted into the EcoR1 and Xba I sites of the eukaryotic expression vector PCDNA3 (Invitrogen). All cloning was done using standard methodologies. PCR amplification of genomic DNA from AT3 cells with FGF-R2 specific primers Int 3BF2 5'-CCGGACTAGTCACTACCGTTCTCCACCACT-3' (SEQ ID NO:4)and Int 3CR 5'-CCGGCTCGAGGGTCGGAAATCATTCGAAAC-3' (SEQ ID NO:5), and

Intron 1F-5' CCGGACTAGTAAGCCCAAGGGGCCAGCAGT-3' (SEQ ID NO:6) and Intron 3R 5' CCGGCTCGAGACGAAGAG CCAAGGGCGCCT-3' (SEQ ID NO:7) yielded fragments FL and FS, respectively (Fig. 1B). These products were digested with Spe I and Xho I and inserted into the Xba I and Xho sites of the pI-11 intron to yield pI-11-FL and pI-11-FS. Constructs derived from intron deletions in pI-11-FS as represented in Fig 4A (for example, pI-11-FS-ΔBcl-I/Nde I) were obtained by first cloning the FS sequences into the Spe I and Xho 1 sites of pBluescript (Stratagene), to generate pBlue-FS since these enzymes cut within PCDNA3 but not pBluescript. Deletions were performed by sequential digestion of pBlue-FS using the indicated restriction endonucleases. The digested ends were blunted using Pfu polymerase (Stratagene) and the resulting plasmids were gel purified, and religated using T4 DNA ligase. These plasmids were digested with Spe I and Xho I and the minigenes were cloned back into the Xba I and Xho sites of pI-11. Plasmids pI-11-IIIb-plus and pI-11-IIIb-minus were obtained using primers Int 3BF2 and Intron 2R2 5'-CCGGCTCGAGGGCTAGACATAGGAATGATT-3' (SEQ ID NO:8) and PCR amplification of pI-11-FS-ΔBcl I/Nde I and pI-11-FS-ΔBcl I/Nsi I, respectively. After Spe I and Xho I digestion the PCR products were cloned into the Xba I and

Xho I sites of pI-11. Plasmids pI-11-IIIc-plus and pI-11-IIIc-minus were similarly obtained by PCR amplification using primers Intron 2F 5' CCGGACTAGTCAACGTTTTTGTGTTTGTGT-3' (SEQ ID NO:9) and Int 3CR to amplify pI-11-FS-ΔBcl I/Nde I and pI-11-FS-ΔBcl I/Nsi I, respectively, followed by digestion with Spe I and Xho I, and insertion into the Xba I and Xho I sites of pI-11. pI-11-FS-Not/Cla-ISAR resulted from PCR of pI-11-FS using primers Nde/Not-F 5'-CCGGCATATGGCGGCCGCC AAACAAATTCAAAGAGAAC-3' (SEQ ID NO:10) and Nsi/Cla-R 5'-CCGGATGCATATCGATGCGATTGAA CACATGGAAAA-3' (SEQ ID NO:11), digestion of these products with Nde Iand Nsi I and cloning into the Nde I and Nsi I sites in pBlue-FS. The minigene sequence was removed with Spe I and Xho I and cloned into the Xba I and Xho I sites of pI-11 to generate pI-11-FS-Not/Cla-ISAR. The ISAR mutant constructs pI-11-Not/Cla: Blue1, SAR 5', SAR 3', SAR-20, Mut 1, Mut 2, Mut 3, Blue2, Rep1, and Rep 3 were obtained by deleting ISAR from pI-11-FS-Not/Cla-ISAR using Not I and Cla I, and then inserting annealed oligonucleotides with complementary Not I and Cla I sites as represented by the following oligonucleotide pairs: Blue1-F:
5'-GGAAGCGACTCCCCGTCGTGTAGATAACTACGATACGGGAGG
GCTTACCATCTGGCCCCAGTGAT-3' (SEQ ID NO:12); Blue1-R:

5'-CGATCACTGGGGCCAGATGGTAAGCCCTCCCGTATCGTAGTTA TCTACACGACGGGGAGTCGC-3'(SEQ ID NO:13); SAR 5'-F: 5'-GGCCGCAAACAAATTCAAAGAGAACGGACTCTGTAT-3' (SEQ ID NO:14); SAR 5'-R: 5'-CGATACAGAGTCCGTTCTCTTTGAATTTGTTTGGC-3' (SEQ ID NO:15); SAR 3'-F: 5'-GGCCGCGGGCTGATTTTTCCATGTGTTCAATCGCAT-3' (SEQ ID NO:16); SAR 3'-R: 5'-CGATGCGATTGAACACATGGAAAAATCAGCCCGC-3' (SEQ ID NO:17); SAR-20-F: 5'-GGCCGCCAAAGAGAACGGACTCTGTGGGCTGATTTTTCCATGTAT-3' (SEQ ID NO:18); SAR-20-R: 5'-CGATACATGGAAAAATCAGCCCACAGAGTCCGTTCTCTTTGGC- 3' (SEQ ID NO:19); Mut1-F: 5'-GGCCGCCAAACTCTACGGACTCTGTGGGCTGATTTTTCCATGTAT- 3' (SEQ ID NO:20); Mut1-R: 5'-CGATACATGGAAAAATCAGCCCACAGAGTCCGTAGAGTTTGGC-3' (SEQ ID NO:21); Mut2-F: 5'-GGCCGCCAAAGAGAACGGACTCTGTGGGCTGAAAGATCCATGTAT 3' (SEQ ID NO:22); Mut2-R: 5'-CGATACATGGATCTTTCAGCCCACAGAGTCCGTTCTCTTTGGC-3' (SEQ ID NO:23); Mut3-F: 5'GGCCGCCAAAGAGAACGGACTCTGTGGGCTGATTTTTCACGCTAT- 3' (SEQ ID NO:24); Mut3-R: 5'-CGATAGCGTGAAAAATCAGCCCACAGAGTCCGTTCTCTTTGGC-3' (SEQ ID NO:25); Blue2-F: 5'-GGCCGCAAGTGGTGGCCTAACTACGGCTACACTAGAAGGACACAT 3' (SEQ ID

NO:26); Blue2-R: 5'-CGATGTGTCCTTCTAGTGTAGCCGTAGTTAGGCCACCACTTGC-3' (SEQ ID NO:27); Rep1-F: 5'-GGCCGCGGGCTGATTTTTCCATGTAT (SEQ ID NO:28); Rep1-R: 5'-CGATACATGGAAAAATCAGCCCGC (SEQ ID NO:29); Rep3-F: 5'-GGCCGCGGGCTGATTTTTCCATGTGGGCTGATTTTTCCATGTGG GCTGATTTTTCCATGTAT-3' (SEQ ID NO:30); Rep3-R: 5'-CGATACATGGAAAAATCAGCCCACATGGAAAAA TCAGCCCACATGGAAAAATCAGCCCGC-3' (SEQ ID NO:31). All plasmid minigenes were prepared using plasmid maxi kits from Qiagen. The identities all minigenes were confirmed by automated DNA sequencing using an ABI sequencer.

Please replace the paragraph beginning at page 23, line 5, with the following rewritten paragraph:

RNA purification and RT-PCR analysis. Total cellular RNA was isolated from transfected cells using the method of Chomczynski and Sacchi. 2 μg of total RNA were heated to 100°C, chilled on ice, and reverse transcribed in a reaction volume of 20 μl. containing 50 mM Tris-HCl (pH 8.3), 75mM KCl, 3mM $MgCl_2$, 10 mM DTT, 1mM dNTPs, 100 ng random hexamers, 2 U Rnasin (Promega), and 200 U MMLV-RT (Gibco) at 37°C for 1 hour. Samples were then heated to 90°C for 5 minutes, then chilled on ice. 2 μl of each

reverse transcription reaction was amplified in a 100 μl PCR reaction containing 50 mM KCl, 10 mM Tris-HCl (pH 8.8), 1.5 mM $MgCl_2$, 0.1% gelatin, 200 μM dATP, dGTP, and TTP, 50 μM dCTP, 100 nM each primer, 10 μCi [α-^{32}P] dCTP, and 2.5 U Taq DNA polymerase (Boehringer Mannheim). Primers used were FGF-FB: 5'-CCCGGGTCTAGATTTATAGTGATGCCCAGCCC-3' (SEQ ID NO:32) and FGF-RB: 5'-CCCGGGGAATTCACCACCATGCAGGCGATTAA-3' (SEQ ID NO:33) for analysis of the endogenous gene and standard T7 and SP6 promoter primers for analysis of transfected minigenes. Amplification conditions consisted of an initial denaturation at 94°C for 4 minutes, followed by 40 cycles of denaturation at 94°C for 30 seconds, annealing at 65°C for 30 seconds, and extension at 72°C for 1 minute, and a final extension at 72°C for 7 minutes. In all amplifications reactions, a water control and a mock reverse transcription control was included which resulted in no PCR product in all experiments. PCR products were directly added to restriction endonuclease digestions with either Ava I or Hinc II (New England Biolabs). Complete digestion using this protocol was always observed. Aliquots representing equal amounts of each PCR reaction with undigested and digested PCR products were loaded directly on 5% polyacrylamide non-denaturing gels at 100V for 3-4 hours, followed by drying and exposure to Amersham

Hyperfilm-MP. Phosporimager analysis was performed using a Molecular Dynamics Phosphorimager. Because equal amounts of Ava I and Hinc II digested PCR products were loaded onto each gel, quantification of exon IIIb or IIIc containing cDNAs (UBD or UCD) were obtained by using the quantification of the band at 380/377 bp which remained following Hinc II or Ava I digestion, respectively, as the numerator. The denominator consisted of the sum of the bands remaining at 380/377 bp for each digest (UBD+UCD). When these results were also expressed with the contribution of IIIb and IIIc skipped products, the average value of the 232 bp band was also used in the sum of the denominator (UBD+UCD+UD), corrected for molar equivalents. Quantification of experiments using minigenes with only one (IIIb or IIIc) internal exon was determined as the sum of the 380 or 377 bp band divided by the sum of this same band and the 232bp band corrected for molar equivalents.

Please replace the paragraph beginning at page 25, line 2, with the following rewritten paragraph:

Nucleotide sequences of the introns flanking alternative exons IIIb and IIIc are highly conserved between rat and human. Because phylogenetic sequence comparisons often help to identify sequences with important

functions, genomic DNA was sequenced from the regions of both rat and human FGF-R2 genes containing the alternative IIIb and IIIc exons, the constitutive exons located upstream and downstream of them, and the three introns between these exons. As seen in Fig. 1 the intron sizes flanking the alternative exons are roughly 1.1, 1.2 and 1.9 nucleotides in both rat and human genomic sequences. Henceforth, these exons will be referred to as intron 1, intron 2, and intron 3, respectively. The University of Wisconsin Sequence Analysis Package GAP program was used to align the rat and human sequences for direct sequence comparison. As expected, the exon sequences were highly similar and corresponded to previously reported cDNA sequences for rat and human FGF-R2. Interestingly, the introns contained a number of regions with a very high level of sequence similarity and these regions were clustered around the IIIb and IIIc exons, whereas the intron sequences adjacent to the constitutive exons did not show an appreciable level of similarity. The rat sequence was screened and all intronic regions in which 90% of the nucleotides were identical to the corresponding human sequence for a stretch of at least 20 consecutive nucleotides were highlighted. These data are presented graphically in Fig. 1B. While some of these regions may

represent evolutionary vestiges, it was also expected that regulatory sequences involved in mediating alternative splicing of these exons, which have been conserved from rat to human, would likely be represented by such conserved sequences. Thus, this information was used to direct the construction of a variety of minigenes, described below.

Please replace the paragraph beginning at page 26, line 9, with the following rewritten paragraph:

Minigenes pI-11-FL and pI-11-FS recapitulate the splicing pattern of the endogenous gene in AT3 and DT3 cells. An RT-PCR based assay was used that is similar to one used by other researchers investigating splicing of human FGF-R2 to assay for the splicing pattern of exons IIIb and IIIc. For analysis of the endogenous FGF-R2 transcript, RT-PCR was performed using primers (FGF-FB and FGF- RB) specific for the constitutive exons located upstream of IIIb and downstream of IIIc as shown in Fig. 2A. These products were separately digested with Ava I and Hinc II and analyzed by gel electrophoresis as demonstrated in Fig. 2B. Because exon IIIb contains an Ava I site not present in IIIc and exon IIIc contains two Hinc II sites not present in IIIb, IIIb inclusion is expected to result in a 367 bp product which is cut with Ava I but not Hinc

II, and IIIc inclusion to result in a 364 bp product which is cut only by Hinc II. As expected, DT3 cells produce an FGF-R2 transcript which contains exclusively exon IIIb and AT3 cells consist entirely of IIIc containing transcripts; results which are consistent with the original report describing alternative splicing of FGF-R2 in these cells. The validity of this assay was tested by performing the same assay using titrations in which RNAs that contained only exon IIIb were mixed with RNAs containing only exon IIIc and it was observed that the proportion of each isoform seen by RT-PCR directly correlated with the fraction of the same isoform in the mixture. Thus, mRNAs containing exon IIIb or IIIc were amplified with equivalent efficiency in this assay. Furthermore, sequencing of these RT-PCR products verified that they were correctly identified by this approach.

Before the Figures, substitute the Sequence Listing submitted herewith for that submitted February 12, 2001.

IN THE CLAIMS:

Cancel claims 1-4 and add the following new claim in lieu thereof.